REMARKS

Reconsideration of the application in view of the above amendments and the following remarks is respectfully requested.

Claims 1-43 are presently pending in the above-identified application. As discussed in more detail below, claims 1-43 are canceled. Claims 44-90 are newly added. Accordingly, upon entry of the this amendment, claims 44-90 are pending.

Compounds considered as fully enabled by the Examiner:

The examiner has indicated that compounds 2 and 9 are fully enabled by the specification, as are the complexes formed by compound 2 and/or 9 with the DNA methyltransferases M.Taq1 or M. Hha1. New claims 67 and 68 are directed to compounds 2 and 9, respectively. New claims 73-75 are directed to complexes formed by compound 2 with M.Taq1, M. Hha1 and compound 9 with M.Taq1, respectively. Because the Examiner cites no prior art, they are considered novel and non-obvious. Accordingly, new claims 67-68, 73-75 are clearly allowable.

Item 7 of the Office Action:

The Examiner rejected Claims 1-15 and 27 under 35 U.S.C. §112, first paragraph, for failing to provide enablement for the genus of compounds of formula (I) as set forth in the currently pending claims.

In his Office Action, the Examiner maintained that the scope of the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims". Applicants respectfully traverse.

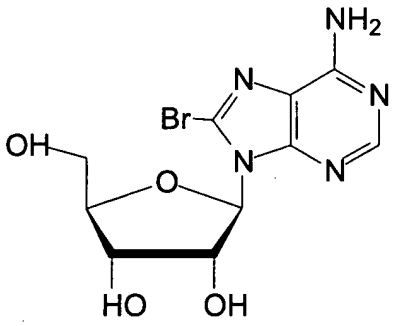
Without acquiescing to the Examiner's position, Applicants have canceled claims 1-43. New claims 44-68 are directed to compounds of the invention and new claims 82-89 are directed to the methods of using the compounds of the invention. Applicants submits that the new claims are fully enabled by the specification as it was originally filed. Additionally, Applicants submit herewith a newly executed §1.132 Declaration by Dr. Elmar Weinhold which

presents detailed evidence to further explain the enablement of new claims 44-90 by the specification as originally filed.

Specifically with respect to the "how to make" prong of the enablement requirement, Applicants believe that the synthetic schemes and experimental data as disclosed in the specification can be readily used by one skilled in the art, armed with the knowledge of standard organic chemistry reactions and reagents, to prepare all the compounds covered by the new Claim 44 without undue experimentation.

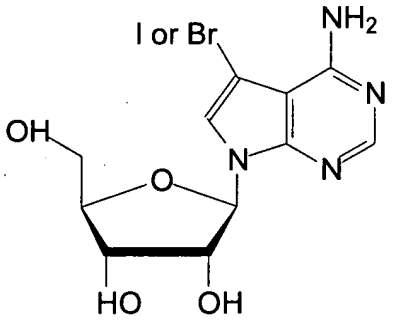
In particular, Reaction Scheme 6 of the Specification allows for all of the compounds within the scope of new claims 44-68 to originate from either 8-bromo adenosine (the precursor to the starting material in Reaction Scheme 6) or 7-iodo(or bromo)-7-deaza adenosine. Both of these compounds (shown as Formula (IIa) and (IIb) below) were commercially available at the time of the invention and were known precursors in the preparation of adenosine analogs and derivatives.

(IIa)



8-bromo adenosine

(IIb)



7-iodo(or bromo)-7-deaza adenosine
also called 5-iodotubercidin

Specifically, Reaction Schemes 6 and Example 2 detail the step-by-step preparation of a compound of claim 44 wherein Y is N and R^1 is a diamine-linked fluorophore, i.e., -NH(CH2)$_4$NH-Dansyl. One skilled in the art, based on the teaching provided by Reaction Scheme 6, will readily appreciate that to prepare any other compounds of Formula (I) wherein Y is N, one can employ the commercially available 8-bromo-adenosine (IIa) and follow the steps of Reaction Scheme 6, using an appropriate diamine and R^4 group to arrive at a final product. Similarly, for compounds of Formula (I) wherein Y is CR^3 and R^1 is hydrogen, one skilled in the art will logically recognize that the starting material can be an analog of 8-bromo adenosine, i.e.,

7-iodo (or bromo)-7-deaza adenosine (IIb), and follow the same reaction steps as taught in Reaction Scheme 6. In other words, as further set forth in details in the Declaration, each step in Reaction Scheme 6 may be generally applied by one skilled in the art to either adenosine starting materials to produce the desired final product.

Similarly, one of ordinary skill in the art will readily recognize that replacing the aziridine in Reaction Scheme 6 with an aziridine substituted with an alanine derivative will provide a compound of Formula (I) where R^2 is $-CH_2CH(COOH)(NH_2)$. The Declaration provides detailed evidence that such a substituted aziridine can be prepared by one skilled in the art using known methods at the time of the invention.

Moreover, an organic chemist of ordinary skill will reasonably expect to have to adjust the reaction conditions and parameters in order to achieve optimal results in terms of yield and purity. Such adjustment are routinely performed by organic chemists and would not rise to the level of "undue experimentation". Applicants therefore respectfully submit that the synthetic scheme of making the compounds of the invention, as set forth in Reaction Scheme 6, and the specific examples in the Specification for preparing the specific compounds of the invention provides sufficient guidance for one skilled in the art to make all the compounds within the claimed subject without undue experimentation.

With respect to the "how to use" prong of the enablement rejection, the Examiner specifically alleged that one of ordinary skill in the art would be required to "screen a large number of alternative protocols to determine if the synthesized species would act as a cofactor for a SAM-dependent methyltransferase".

Applicants believe that the teachings of the specification, in view of the factual evidence presented in the Declaration, clearly provide the necessary guidance to one skilled in the art to determine how to use the claimed compounds. In particular, the experimental section of the specification provides a detailed description for preparing the enzymes M Taq 1 and M Hha 1, conducting enzymatic reactions and identifying the products by mass spectroscopy. Biochemists and molecular biologists routinely conduct and indeed, expect to conduct the testing and screening of compounds of interest according to an established protocol referenced in a publication or as here, a patent.

Furthermore, the underlying principle of the instant invention is that SAM-dependent methyltransferases are also suitable enzymes for transferring the compounds of Formula (I) to a given substrate. This principle is described in detail in the specification. Accordingly, the screening protocols for the claimed compounds can be the same as those that are used when SAM itself is used as a cofactor. There had been an abundance of teachings at the time the specification was filed on various assays which could be used to determine the utility of SAM-dependent methyltransferases (see, for example, the references listed in Appendix I). Applicants are not required to reiterate in the specification that which was known at the time the application was filed. Accordingly, Applicants submit that the teachings of the specification in combination with what was known at the time the application was filed provide sufficient guidance to one skilled in the art on how to use the compounds for the claimed utility.

Item 8 in the Office Action:

The Examiner further rejected Claims 9-10 and 13 under 35 U.S.C. §112, first paragraph, for failing to enable the complexes formed by compounds of formula (I) with methyltransferases other than the DNA methltransferases, i.e., M Taq 1 and M Hha 1. New claims 69-77 are directed to a complex comprising a compound of Formula (I) and a methyltransferase capable of using SAM as a cofactor. Applicants respectfully submit that one skilled in the art, based on the teaching of the specification in connection with the use of M Taq 1 and M Hha 1, will know how to use methyltransferase other than the two that are specifically disclosed. The rationale lies in the fact that it had been well established in the art that SAM dependent methyltransferases are capable of transferring methyl groups from the co-factor SAM to such diverse substrates as DNA, RNA, protein, peptide and even small molecules. The specification specifically cites various references supporting this fact (see, for example, the references listed in Appendix I). These SAM dependent methyltransferases all share a common catalytic domain for SAM. The instant invention teaches that the compounds of formula (I) behave in substantially the same manner as SAM in the presence of two particular DNA methyltransferase, M Taq1 and M Hha1. This result would lead one skilled in the art to reasonably expect the claimed compounds will occupy the same catalytic domain and function in

a similar manner for other SAM dependent methyltransferases. We therefore submit that even though the specification only exemplifies the use of M Taq1 and M Hha1 in the claimed complex, given the teachings provided by the specification, one of ordinary skill in the art would reasonably expect that other methyltransferases would have a similar utility when complexed with the compounds of the invention.

Item 9 of the Office Action:

The Examiner has rejected Claims 1-15 and 21-27 under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner alleged that the phrases such as "amino acids which may optionally be modified", "modified amino acids", "derivative thereof", "aldehyde derivative" and "small molecules" render the claims in which they appear indefinite.

In new claims 44-68 and 82-89, Applicants have canceled the phrases "amino acids which may optionally be modified", "modified amino acids", "derivative thereof", and "aldehyde derivative". With respect to the phrase "small molecules", because it is used in the application in connection with a particular type of methyltransferase, *i.e.*, those methyltransferases that use a small molecule as the substrate, Applicants believe that one skilled in the art will readily recognize what this phrase encompasses in view of the context in which it is presented. Thus, one of ordinary skill in the art would understand the metes and bounds of the claimed subject matter when this phrase is used.

Item 11 of the Office Action:

The Examiner has rejected Claims 16-19, 21-26, 28-41 and 43 under 35 U.S.C. §112, first paragraph, for failing to enable one skilled in the art for making or using the claimed subject matter.

New claims 78-79, 80-81, and 82-90 are the kit, composition and method claims directed to the compounds of Formula (I) as newly defined. Because Applicants believe that the new compound claims overcome the Examiner's rejections under §112, first paragraph, the

corresponding new claims directed to the kit, composition and method of use are similarly patentable under 35 U.S.C. §112, first paragraph.

With respect to the Examiner's position that the state of the art is unpredictable, particularly in light of Applicants' own disclosure in that both the 7- and the 8-position of the adenosine component had been observed to be partly accessible to solvent and that no pattern between "derivatives in the 7 or 8 position and specificity for a broad class of methyltransferases" had been established, Applicants respectfully disagree. Applicants believe that the section of the disclosure to which the Examiner referred serves, in fact, as providing a teaching and guidance to one skilled in the art on how to ascertain which compound of formula (I) should be employed in the invention. In other words, the specification teaches that if the 7-position is accessible to the solvent, *i.e.*, the 7-position does not completely fit into the catalytic domain of a methyltransferase and will therefore likely tolerate a variety of substituents without affecting the catalytic activity of the enzyme, then a compound of the invention with a 7-substitution on the adenosine component should be a viable cofactor for the purpose of this invention. Therefore, by providing this type of teaching, the specification actually injects predictability into the art, thereby enables one skilled in the art to make and use the present invention.

Item 12 of the Office Action:

The Examiner has rejected Claims 16-19, 28-43 under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. In particular, the Examiner alleged that the phrases such as "amino acids which may optionally be modified", "modified amino acids", "derivative thereof", "aldehyde derivative" and "small molecules" render the claims in which they appear indefinite.

As discussed above, Applicants have removed all but "small molecules" from the new set of claims. The phrase "small molecules" does, for reasons set forth above, particularly point out the subject matter Applicants deem as their invention because the phrase was used in connection with particular types of methyltransferase. Given the state of the art, one skilled in the methyltransferase art will recognize what "small molecules" are referred to.

In conclusion, Applicants respectfully submit that, in view of the application as filed and the factual evidence as presented by Dr. Weinhold in his Declaration, the new claims find full support in the specification in terms of "how to make" and "how to use" the claimed compounds. Based on the teachings and guidance as detailed in the specification, one skilled in the art can readily prepare and make use of all the compounds within the scope of the claims without undue experimentation.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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CJR:cew

Enclosures:
Declaration Under 37 CFR 1.132
Appendix I, which includes: *Archives of Biochemistry and Biophysics* 310 (2), 417-427, 1994; *J. Mol. Biol.* 247 (1), 16-20, 1995; *Nucleic Acids Research* 25 (14), 2702-2715, 1997; *Structure* 5, 545-558, 1997; and *Nucleic Acids Research* 25 (14), 2702-2715, 1997

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